AstraZeneca

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December 13, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: *Docket No.: 99D - 3082*
International Conference on Harmonization Topic E10: "Choice of Control Group in Clinical Trials"

Dear Sir or Madam:

Reference is made to the September 24, 1999 Federal Register notice announcing the availability of the above mentioned draft guidance.

AstraZeneca has reviewed this guidance and our comments are attached.

Thank you for your consideration.

Sincerely,

Elizabeth Fenna
Senior Regulatory Project Manager
Regulatory Affairs

99D-3082

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Comments on International Conference on Harmonization Topic E10:

"Choice of Control Group in Clinical Trials",

FDA Docket Number 99D - 3082

Introduction

This topic is vitally important to the R&D-based pharmaceutical industry that creates the vast majority of new active substances, namely the companies which operate globally. Agreement across the three ICH regions on the selection of a single set of control groups acceptable to them all would be the greatest single contribution that ICH could make to:

- saving costs of drug development
- saving time to market
- reducing the duplication of patient groups requiring clinical study before a product may be submitted for marketing approval
- enabling a common technical dossier for the authorization of new medicines.

The comments below are in three sections:

- General comments on the document
- Points of technical critique
- Detailed textual comments

General Comments

Although we consider this document to be of value as a primer for clinical study design, it does not address the most significant issue which ought to be addressed by "The International Conference on **Harmonization of Technical Requirements for Registration** of Pharmaceuticals for Human use" (sic.); - namely the selection of control groups in the various phases of a clinical program that would be acceptable to regulatory authorities across the three regions. Indeed by its own admission (Section 1.1) "this guideline does not address the regulatory requirements in any region, but describes what studies using each design can demonstrate" - it therefore singularly fails to satisfy the basic purpose of ICH. Without

agreement on this topic it remains necessary to satisfy the personal preferences of different groups of assessors for e.g. placebo controls or active controls.

The document serves to explain the strengths and weakness of the different options, but does not say which is preferred in order to demonstrate efficacy and safety for new medicines. The current scope for widely differing preferences by the separate agencies remains. The industry needs the regions of ICH to agree publicly the study comparators acceptable and preferred for Phases II and III in particular, with clear statements of those categories and situations when an exception is warranted.

Specifically:

- The guideline does not resolve the divergent historic preferences of FDA and EU for placebo comparator and active comparator, respectively.
- The guideline gives no indication to the selection of an "international reference drug" as the active comparator.
- The guideline ought to clarify the acceptability of foreign trials against a comparator, which is either not preferred or not approved in the receiving region.
- The guideline should address the circumstances where different doses of an active comparator are authorized in different regions, and define a basis for selecting the "harmonized dose level". A similar proviso relates to the different presentations of an active comparator available in the different regions and even within regions (e.g. EU)
- The guideline should address the differences between the signatory regions in their preferences for "maximum effective dose" or "minimum effective dose" when selecting controls.

The guideline should establish the basis of agreement between the regions on the content of a single clinical program acceptable to all participating regions, with rationale, justification statements etc. Specific issues pertaining to individual therapeutic categories could be addressed eventually in the therapeutic guidelines being considered under ICH topic E11.

- The guideline should address how an optimal programme is built up, rather than focusing at the study level - the study design is determined by the objectives, but the objectives are subsumed into the programme. If ICH is to meet its objective of reducing waste and duplication it needs to address how to minimize the number of comparator studies.

- The document needs to be restructured to allow the contents to be accessed more easily. This includes cross referencing other guidelines, avoiding repetition, less use of sub-sections, use of graphs to illustrate the text, use of a glossary, use of consistent terminology, avoid double negatives, allocation of specific sections to different trial designs and addition of summaries.

In summary the guideline reads like a text on what is achievable by each different type of trial design/ selected control. Instead it should be giving guidance to all pharmaceutical industry personnel about the agreements that have been reached within ICH as to which control is required for success.

Technical Critique

1. Assay sensitivity and sensitivity to drug effects

Two quality criteria are described for the evaluation and interpretation of a non-inferiority trial. This part of the guideline is repetitive and difficult to understand. It needs revision to become more stringent and easily understood.

Part of the confusion is due to the non-descriptive terms introduced; "sensitivity-to-drug-effects" and "assay sensitivity". "Sensitivity to drugs" refers to the assumption that the active control should have reliably demonstrated a difference against placebo in earlier trials with the same features as planned for in the non-inferiority trial. The term "Active control validity" (for the intended purpose) would better capture the desired property. This is a concept, which applies to the design of a trial and clear guidance is required on how this concept should be documented in the protocol.

"Assay sensitivity" associates more to a bioanalytical property than to clinical trials. A more direct term would be "Difference detecting ability" or study design validity, which could be used to mean a valid design/conduct of the study to be able to detect a relevant difference if it exists. This is a concept which applies to the reporting of a trial and clear guidance is required on how this concept should be documented in the report.

In the last sentence of 1.5 it is indicated that assay sensitivity presupposes sensitivity-to-drug-effects. This is confusing. These two quality criteria should be regarded as separate and independent properties, which have to be satisfied simultaneously in order to have a valid non-inferiority study design with the objective to indirectly demonstrate superiority over placebo. If the active control drug chosen lacks sensitivity-to-drug-effects the study as such could still have assay sensitivity.

2. The negative attitude towards non-inferiority trials

The negative attitude towards non-inferiority trials to prove efficacy is inappropriate and needs to be re-addressed. The alternatives indicated are either addressing a different question, such as the randomized withdrawal and early escape designs, and/or require often unrealistic sample sizes, such as add-on or superiority trial designs. The three-arm design with test, active control and placebo is obviously not an alternative if placebo is unethical. It is only useful when the primary objective is to compare the test drug with an active comparator, and a placebo control is ethical.

The description of advantages and disadvantages of placebo-controlled trials in (2.1.6) seems biased. In particular the difficulties with regard to ethics, practicalities, and generalisibility are underestimated as they appear in real life.

Often in drug development it is important to show improvement over a standard treatment with regard to some aspect of a test drug, e.g. safety/tolerability, while not losing anything or only little on the efficacy side. Alternatively, the aim is to show small improvements to current therapy, which accumulated over time, could represent a substantial benefit to patients. These objectives are difficult to fulfill without the use of active control studies, essentially based on a non-inferiority design. The validity of such designs could be highly improved using a prospective meta-analysis approach, i.e. a planned combination of several studies addressing a common question. The document should discuss such issues indicating an understanding of the reality of drug development today.

The issues concerning drug development in Japan are not adequately addressed. Placebo is often inappropriate in Japan and sometimes there is no clear evidence in Japanese populations of active controls. The guideline should state how evidence of active controls can be obtained in these cases, e.g. from other populations.

3. Estimation and Data Interpretation

This section has too much emphasis on significance testing as opposed to estimation and interpretation. The approach of talking only about significance is misleading and unhelpful. There should be greater emphasis on the use of confidence intervals and the reliability and reproducibility of the findings. Many of the concepts on non-inferiority and superiority have been described very well in the CPMP Points to Consider paper on Non-inferiority, superiority, and equivalence. This document would benefit from using some of the clear descriptions, diagrams, and terminology used in the CPMP document.

4. CPMP Points to Consider Paper on superiority, non-inferiority and equivalence.

If the issues described in the CPMP points to consider paper are acceptable to all the regions it would be helpful to include them in this document.

Detailed textual comments:

Randomization

Section 1.2 and 1.2.1: To say that randomization and blinding 'prevent bias' and 'assure groups are similar' seems too strong as they just minimize the chance of differences, particularly if stratified randomization is adopted.

No treatment

There seems to be confusion in the use of the terms no treatment and placebo. Also the examples of no treatment appears inconsistent with the issue described in the text. E.g. Section 1.3.1, 1.3.2 and 2.2

Dose Response

Greater clarity is required in the discussion of these studies (Section 1.3.3). It is important to be explicit that comparisons need to be between the randomized groups and not the dose selected groups.

Patient Population

1.4.2.2.2 - Add: "The proper selection of the patient population is critical to the labeled indication for a product. If the patient population is a sub-group of a more generalized patient population, drug sponsors run the risk of the labeled indication referring to this specific sub-population instead of the more generalized patient population."

Unequal randomization

Section 2.1.5.1.1

The relevance of this discussion is unclear. It does not affect the *choice of control*, rather is a consideration in the design of study and allocation of patients. Increasing the size of the active control groups will increase the power of the study although the relative increase in power will be less than would have been if the additional patients were allocated equally to placebo and active

control. The placebo group still needs to be large enough to estimate the placebo response with the required degree of precision. The sample size calculation may well give a lower number than necessary for this (the actual number required for precision is usually arrived at using intuition or "feel"). If the placebo response is very variable a small placebo group could lead to an inflated estimate of the placebo response. As the active groups are larger, and can estimate response with more precision, the placebo response component of the active groups may not be of the same order. Therefore, you could have a large placebo response that will not necessarily be reflected in the active groups. This could lead to the study not detecting differences between active and placebo.

Selection of doses

Section 2.1.6.3 The comment that 'designers of dose response studies need to guess the shape and position of the dose response curve' is inappropriate in this context. All studies require dose selection and if the doses are selected wrongly the use of subjects in the trial may be wasteful.

Dose response Studies

Section 2.3.7 It is not possible to conclude that the largest doses are effective as implied here. Theoretically, if a study has established a positive trend, in other words, a significant positive slope in a regression analysis, then every dose gives rise to a different response however small the differences are in response between doses. Which doses are effective depends on clinical judgement and the minimally effective dose(s) would probably have to be studied further in a confirmatory clinical trial. (Assuming that the objective of the dose-response study was to choose a safe and effective dose for study in a confirmatory study).

2.1.7.3 Generalizability

Final sentence - as this is supposed to be a guideline, it is unhelpful to have sentences that confuse the guidance - we need the judgement of the ICH group on the significance of the situation being described, particularly if this has to be a matter of opinion rather than specifically justified.

2.1.7.1

Ethical concerns: Even in situations when effective therapy is known and an add on placebo controlled study is fully ethical. This needs to be clarified.**2.5.2**

1st paragraph: "criteria that are generally more stringent and identify a less sick population than is typical of external control groups. The group is often identified retrospectively, leading to potential bias in its selection." Should "less" be "more"? In addition, "The group is often identified..." would be clearer to say, "The external control group is often identified..."

2.5.3

2nd paragraph: "as the estimate of control group": Does this mean "as the estimate of the historical control group"?

Figure 1 Choosing the concurrent control for demonstrating efficacy

2nd box on the left - please insert "proven effective .. " before "treatment" … in order to minimize confusion.

December 3, 1999

Final

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